

Epidemiology of Hypertrophic Cardiomyopathy–Related Death

Revisited in a Large Non–Referral-Based Patient Population

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Background—Death resulting from hypertrophic cardiomyopathy (HCM), particularly when sudden, has been reported to be largely confined to young persons. These data emanated from tertiary HCM centers with highly selected referral patterns skewed toward high-risk patients.

Methods and Results—The present analysis was undertaken in an international population of 744 consecutively enrolled and largely unselected patients more representative of the overall HCM spectrum. HCM-related death occurred in 86 patients (12%) over 8 ± 7 years (mean \pm SD). Three distinctive modes of death were as follows: (1) sudden and unexpected (51%; age, 45 ± 20 years); (2) progressive heart failure (36%; age, 56 ± 19 years); and (3) HCM-related stroke associated with atrial fibrillation (13%; age, 73 ± 14 years). Sudden death was most common in young patients, whereas heart failure– and stroke-related deaths occurred more frequently in midlife and beyond. However, neither sudden nor heart failure–related death showed a statistically significant, disproportionate age distribution ($P=0.06$ and 0.5 , respectively). Stroke-related deaths did occur disproportionately in older patients ($P=0.002$). Of the 45 patients who died suddenly, most (71%) had no or mild symptoms, and 7 (16%) participated in moderate to severe physical activities at the time of death.

Conclusions—HCM-related cardiovascular death occurred suddenly, or as a result of heart failure or stroke, largely during different phases of life in a prospectively assembled, regionally based, and predominantly unselected patient cohort. Although most sudden deaths occurred in adolescents and young adults, such catastrophes were not confined to patients of these ages and extended to later phases of life. This revised clinical profile suggests that generally held epidemiological tenants for HCM have been influenced considerably by skewed reporting from highly selected populations. These data are likely to importantly affect risk stratification and treatment strategies importantly for the prevention of sudden death in HCM. (*Circulation*. 2000;102:858-864.)

Key Words: cardiomyopathy ■ death, sudden ■ heart failure

Hypertrophic cardiomyopathy (HCM) is a complex primary and genetically transmitted cardiac disease with a diverse clinical course that includes a benign or stable clinical course over many years, progressive congestive symptoms requiring therapeutic intervention, and the possibility of sudden and unexpected death.^{1–9} Since the initial description of HCM in 1958,¹⁰ sudden death occurring in young and usually asymptomatic patients has received substantial exposure in the literature as the most devastating consequence of the disease.^{11–21} However, until recently, natural history data for HCM were predominantly assembled at a few large, tertiary centers with patient referral patterns preferentially

comprised of high-risk patients.^{1–3,6,7,21,22} In the present study, we have reassessed the epidemiology and clinical profile of HCM-related death in a largely unselected cohort of 744 patients that more closely reflects the overall clinical spectrum of the disease.

Methods

Patient Selection

Patient populations from 3 regional centers were combined to assemble a consecutive cohort of 744 patients evaluated between 1975 and 1998: (1) the Minnesota cohort: 297 patients from the Minneapolis Heart Institute and Children's Heart Clinic, consisting

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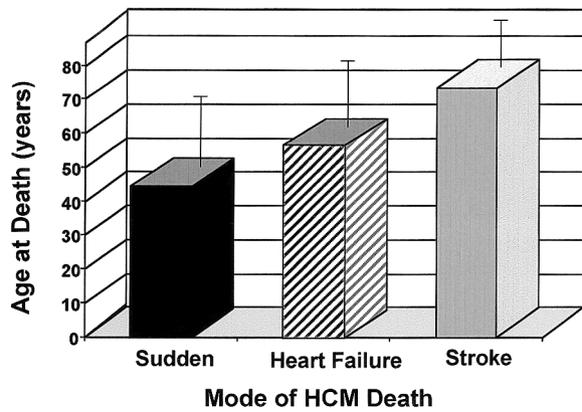


Figure 1. Ages at which 3 modes of HCM-related death occurred in 86 patients. Twenty patients who survived cardiac arrest (or had appropriate ICD intervention) or were heart transplant recipients are regarded as equivalent to sudden or heart failure-related death, respectively.

primarily of Minnesota residents but also those from the adjacent states of Wisconsin, Iowa, and North and South Dakota⁷; (2) the Tuscany cohort: 237 patients, predominantly from the region of Tuscany in central Italy and the Careggi Hospital in Florence²³; and (3) the Genoa cohort: 210 patients from metropolitan Genoa and adjacent regions of northwestern Italy and the Galliera Hospital.²⁴ The period of follow-up from first hospital evaluation for the overall study group was 8.0 ± 7 years. Portions of these databases have been used in other clinical studies.^{7,23,24}

Echocardiography

Echocardiographic studies were performed with commercially available Hewlett-Packard and Toshiba instruments. Left ventricular hypertrophy was assessed with 2-dimensional echocardiography, and the site of maximum wall thickness was identified.^{25,26} Peak instantaneous left ventricular outflow gradient was estimated with continuous-wave Doppler under basal conditions.²⁷

Statistical Analysis

Data are expressed as mean \pm SD. Differences between means were analyzed with 1-way ANOVA with the Bonferroni test for post hoc group comparisons or unpaired Student's *t* test, as appropriate. The uniformity of age distributions at death was assessed statistically by use of the nonparametric Kruskal-Wallis test. Comparison of nominal variables expressed as proportions were performed by use of the Pearson χ^2 test.

Definitions

HCM

The diagnosis of HCM was based on the 2-dimensional echocardiographic identification of a hypertrophied, nondilated left ventricle (wall thickness ≥ 15 mm in adults and the equivalent relative to body surface area in children)²⁸ in the absence of another cardiac or systemic disease capable of producing the magnitude of wall thickening evident.²⁹

Sudden cardiac death was defined as unexpected sudden collapse occurring < 1 hour from the onset of symptoms in patients who had previously experienced a relatively stable or uneventful clinical course. In addition, potentially lethal cardiovascular events in which 14 patients either were successfully resuscitated from cardiac arrest (with documented ventricular fibrillation; $n=11$) or received appropriate defibrillation shocks from an implanted cardioverter-defibrillator (ICD; $n=3$) were regarded as equivalents of sudden cardiac death in the present data analysis. Two patients who survived

their first cardiac arrest ultimately died in refractory heart failure 34 months and 17 years later but are tabulated as sudden deaths for the purposes of this study.³⁰

Congestive heart failure-related death was defined as occurring in the context of cardiac decompensation and progressive disease course ≥ 1 year before death, particularly if complicated by pulmonary edema or evolution to the end-stage phase³¹ and/or requiring hospitalization for heart failure. Seven patients with advanced refractory heart failure who received heart transplants³² were considered equivalent to HCM-related heart failure deaths in this analysis.

Stroke-related deaths were judged to be a direct consequence of embolic or other events related to HCM, usually in the setting of paroxysmal or chronic atrial fibrillation.³³

Results

Demographics

Clinical and demographic variables are tabulated for the overall patient population and individually for each of the 4 patient cohorts in Table 1. The vast majority of these parameters were similar among the 4 populations. However, patients from Minnesota and Genoa had been treated with amiodarone less frequently than were the patients from Tuscany (Table 1).

Mode of Death

Of the 744 study patients, 125 (17%) died during the follow-up period. These included 36 from causes unrelated to HCM (such as cancer, suicide, accident, or acute myocardial infarction resulting from advanced coronary artery disease); 3 others occurred perioperatively as a result of complications of ventricular septal myotomy-myectomy. In the remaining 86 patients, death was judged to be probably or definitely a result of HCM, although 3 of these patients also had atherosclerotic coronary artery disease documented during life or at autopsy.

Three modes of death were defined (Figure 1 and Table 1): (1) sudden and unexpected (44 patients, including 11 with aborted cardiac arrest and 3 with appropriate ICD interventions for ventricular tachycardia or fibrillation); (2) resulting from progressive, refractory heart failure (31 patients, including 8 with heart transplantation)³²; and (3) as a consequence of HCM-related ischemic stroke, largely compatible with a cardioembolic origin (11 patients; Figure 1 and Table 2). Three other patients died postoperatively after ventricular septal myotomy-myectomy operation.¹⁻⁵

Relation of Mode of Death to Clinical Parameters

Age

The distribution of age at death was dissimilar for the 3 modes ($P < 0.001$). In the group analysis for the study population, sudden deaths occurred in the younger patients (mean age, 45 ± 20 years; Figure 1 and Table 1). Nevertheless, with individual patient analysis, the 44 sudden deaths were distributed throughout a wide range of ages (7 to 78 years); 14 (32%) occurred in patients ≥ 35 years of age, but 15 patients (34%) were ≥ 55 years of age (Figure 2). Consequently, the risk of sudden death was not confined to young patients but extended into later phases of life (Figure 2) and without a statistically significant predilection for any

TABLE 1. Clinical and Demographic Features in Regional Populations Comprising 744 Patients with HCM

Parameters	Study Populations			
	Minnesota	Tuscany	Genoa	Combined
Patients, n	297	237	210	744
HCM-related deaths, n				
Total	26	27	11	64
Sudden	17	9	4	30
CHF related	4	14	5	23
Stroke related	5	4	2	11
Aborted cardiac arrest, n	6	7	1	14
Heart transplants, n	5	2	1	8
Age at HCM death, y	59±22	56±23	57±18	58±21
Age at initial evaluation, y	47±22	41±17	47±19	45±20
Duration of follow-up, y	7.7±7	12.0±7	4.3±4	8.0±7
Male sex, n (%)	162 (55)	170 (63)	139 (67)	462 (62)
Severe symptoms,* n (%)	62 (21)	56 (23)	20 (10)	138 (19)
Maximum LV wall thickness, mm	21.7±5	22.8±5	19.3±6	21.4±5
Outflow obstruction,† n (%)	74 (25)	46 (19)	48 (23)	165 (22)
LVED, mm	43±8	42±9	47±5	44±8
Left atrium, mm	42±9	40±10	44±7	42±9
Atrial fibrillation, n (%)	55 (19)	60 (25)	38 (18)	153 (21)
Receiving β -blocking agents, n (%)	140 (47)	104 (43)	44 (20)	288 (39)
Receiving verapamil, n (%)	98 (32)	94 (39)	36 (17)	228 (31)
With amiodarone, n (%)	18 (6)	75 (32)	13 (6)	106 (14)
With antiarrhythmics (other than amiodarone‡), n (%)	9 (3)	37 (15)	3 (1)	49 (7)
With DDD pacing (for gradient/symptoms), n (%)	7 (2)	1 (0.4)	0 (0)	8 (1)
ICD, n (%)	10 (3)	6 (2)	0 (0)	16 (2)
With myotomy/myectomy (or MVR), n (%)	29 (9)	8 (3)	2 (1)	39 (5)

LV indicates left ventricular; LVED, LV end-diastolic cavity dimension; and MVR, mitral valve replacement.

*NYHA functional classes III/IV at most recent evaluation.

† ≥ 30 mm Hg peak instantaneous outflow gradient estimated by continuous-wave Doppler.²⁷

‡Includes disopyramide, sotalol, quinidine, and propafenone.

age group ($P=0.06$). The distribution of sudden deaths was not substantially altered with or without inclusion of the 13 patients with either aborted cardiac arrest or appropriate ICD intervention.

In contrast, the 31 congestive heart failure–related deaths occurred frequently in midlife and beyond (mean age, 56 ± 19 years), with 26 of 31 or 84% in patients >35 years of age. There was no significant difference in the distribution of these deaths among age groups ($P=0.5$; Figure 2). Of these 31 patients, 13 were judged to be in the end-stage phase³¹ (Figure 1 and Table 1).

The 11 deaths related to stroke occurred in patients of the most advanced ages (mean age, 73 ± 14 years; Figures 1 and 2 and Table 1), with 10 of the 11 (91%) >65 years of age at the time of their event (Figure 2 and Table 1). Consequently, the age distribution of stroke-related deaths was skewed significantly to older patients ($P=0.0001$; Figure 2). Ten of

the 11 strokes (91%) were also associated with a history of chronic or paroxysmal atrial fibrillation, suggesting cardioembolic origin (Table 2).

Overall, 30 of the 86 HCM-related deaths (35%) occurred after 65 years of age, including 12 deaths in patients >75 years of age (2 of whom died suddenly).

Sex and Family History

No significant differences in sex were evident between patients who died suddenly or of heart failure (Table 2). However, a striking predominance of women (9 of 11 patients; 82%) experienced stroke-related death. Of the 86 patients who died, only 15 (17%) had a family history of ≥ 1 relative with HCM-related death.

Left Ventricular Wall Thickness

Maximum wall thicknesses did not differ significantly among the 3 patient subgroups according to mode of death (Table 2).

However, particularly marked hypertrophy (≥ 30 mm) was present in 18 patients, including 9 (20%) of the 44 who died suddenly.

Outflow Gradient

No significant differences in magnitude of the outflow gradient were evident between patients who died suddenly or of heart failure (27 ± 40 versus 22 ± 34 mm Hg, $P = \text{NS}$); however, patients with stroke-related death showed substantially higher outflow gradients (60 ± 53 mm Hg, $P = 0.02$; Table 2).

Antiarrhythmic Drug Treatment

Of the 744 study patients, 106 (14%) received amiodarone (usually 200 mg/d) for ≥ 6 months, including 20 (23%) of the 86 patients who died of HCM, either for nonsustained ventricular tachycardia on Holter ECG or prevention of atrial fibrillation recurrence. Seven of the 44 patients who died suddenly (16%) had been taking amiodarone at the time of death; of the 106 patients taking amiodarone, 10 (9%) experienced heart failure-related death.

Annual Mortality Analysis

Clinical outcome was also prospectively analyzed with respect to annual HCM mortality from the time of study entry (ie, at initial evaluation; Figure 3). Annual mortality for deaths occurring either suddenly and unexpectedly, as a result of heart failure, and as a consequence of stroke or for all HCM-related deaths combined were 0.7%, 0.5%, 0.2%, and 1.4%, respectively. Furthermore, for sudden or heart failure-related deaths, no statistically significant differences in annual mortality were evident with respect to the age groups ($P = 0.10$ and 0.09 , respectively). In contrast, annual mortality resulting from stroke was highest in the oldest patients ($P < 0.001$).

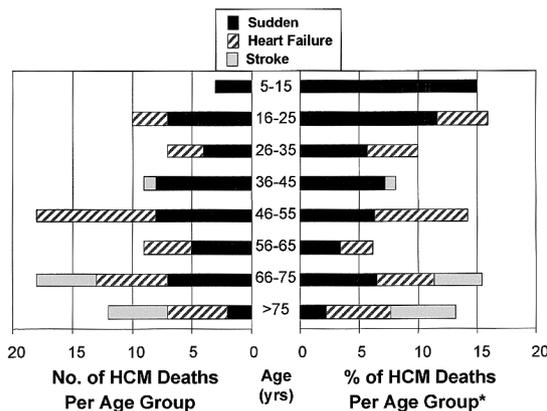


Figure 2. Distribution of ages at time of HCM-related death. Left, Displayed as absolute number of patients with sudden death (or aborted cardiac arrest), death related to heart failure (or requiring heart transplant), or death as consequence of HCM-related stroke. Right, Displayed as percent HCM mortality by age group. For each age group, percent HCM mortality was calculated by dividing total number of HCM deaths by total number of patients at end of follow-up (or at death). Probability values testing uniformity of age distribution for 3 modes of HCM deaths were as follows: sudden death, $P = 0.06$; heart failure-related death, $P = 0.5$; and stroke-related death $P = 0.0001$.

Circumstances of Sudden Deaths

Prior Symptoms

Sudden cardiac death occurred predominantly in those patients with no or mild symptoms (NYHA functional class I and II; 31 of 44 patients, 71%), and 17 of these patients had been asymptomatic before death. The remaining 13 patients (29%) who died suddenly had experienced substantial limiting symptoms (functional class III); however, each was clinically stable and had not experienced progressive deterioration before death (Figure 4).

Prior Activity

Most patients (37, 84%) died suddenly during or immediately after a variety of sedentary or mild physical activities such as watching television, walking, or driving a car (including 7 who died while sleeping in bed); 37 deaths occurred outside the hospital, and 2 inpatients died. The remaining 7 patients (16%) died during moderate to severe physical exertion, including only 1 who had been engaged in competitive athletics (a 33-year-old man in master's level sports who survived a cardiac arrest incurred during burst exertion; Figure 4).

Discussion

This study revisits the epidemiology and profile of death in HCM by using a largely unselected and longitudinally assessed, consecutive population of patients who were previously diagnosed with the disease. This large HCM cohort of ≈ 750 patients differs importantly from tertiary center cohorts in which referral patterns are skewed toward those patients perceived to be at high risk.^{1,3,6,7,21,22} In contrast, our study population was assembled by combining all HCM patients from 3 regional centers virtually free of tertiary center referral bias and therefore was more closely representative of the overall disease spectrum. The relatively low mortality rates reported here for sudden and other HCM-related modes of

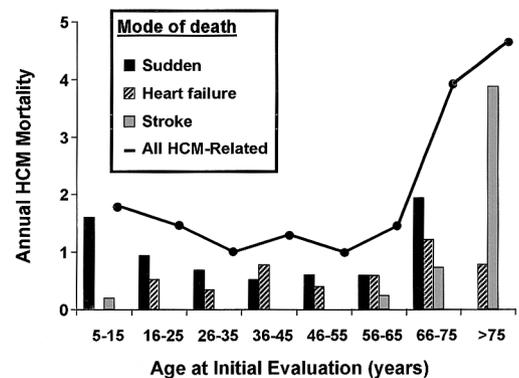


Figure 3. Annual HCM-related mortality depicted prospectively from age at study entry (initial evaluation). Calculated by dividing number of deaths by total number of patients in given age group at initial evaluation, by mean follow-up period for that age group. Continuous line depicts overall HCM mortality related to age at initial evaluation. Probability values testing the uniformity of age distribution at death were as follows: sudden death, $P = 0.01$; heart failure-related death, $P = 0.09$; stroke-related death, $P < 0.001$; and combined, $P = 0.07$.

TABLE 2. Clinical and Demographic Parameters and Mode of HCM-Related Death in 86 Patients

	Patient, n	Age at Initial Evaluation, y	Age at HCM Death, n		Male, n (%)	Maximum LV Thickness, mm	Outflow Gradient,* mm Hg	With Gradient ≥ 30 mm Hg,* n (%)
			<75 y	≥ 75 y				
Sudden death	44	39 \pm 22	42	2	27 (61)	24 \pm 6 (17–40)	25 \pm 39 (0–150)	13 (30)
Heart failure	31	48 \pm 17	27	4	19 (61)	24 \pm 5 (15–34)	22 \pm 33 (0–110)	12 (39)
Stroke	11	67 \pm 22†	6	5	2 (18)‡	24 \pm 5 (18–30)	60 \pm 53‡ (0–146)	7 (64)

LV indicates left ventricular; LVED, LV end-diastolic cavity dimension; LA, left atrial dimension; and AF, atrial fibrillation. Values are n (%) or mean \pm SD (range).

*Peak instantaneous gradient estimated by continuous-wave Doppler.²⁷

† $P < 0.001$ vs heart failure and sudden death groups.

‡ $P < 0.02$ vs heart failure and sudden death groups.

§ $P < 0.001$ vs sudden death group.

|| $P < 0.05$ vs sudden death group.

¶ $P < 0.001$ vs sudden death group.

$P < 0.05$ vs heart failure group.

death (<1%/y) are consistent with the relatively unselected nature of the study group.^{6–8,22,23}

In the present profile, we defined 3 distinctive modes of HCM-related death occurring largely during different periods of life. For example, sudden and unexpected death often occurred in younger patients, although without a clear predilection for any particular age group. Most heart failure–related deaths were in midlife and beyond. Death as a consequence of stroke (usually embolic and associated with atrial fibrillation) was virtually confined to much older patients, many of whom had already achieved normal longevity in statistical terms.

Numerous prior reports from HCM referral centers emphasized that sudden cardiac death (or resuscitated cardiac arrest) preferentially occurred during a particular period of life—ie, in asymptomatic (or mildly symptomatic) children and adults younger than ≈ 35 years of age.^{4,5,11–21,34} Therefore, we have reported a profile of sudden death that modifies in certain important respects the profile previously described for HCM.^{4,5,11–21} In our regional and largely unselected population, we could not replicate prior descriptions of a sharp peak in sudden death during adolescence and young adulthood²¹ and little risk for sudden death after 35 years of age. In contrast, although the present analysis demonstrates a trend toward greater frequency of sudden death among younger patients (adolescents and young adults), these events were neither confined to young patients nor disproportionately distributed across a broad expanse of ages from 7 to 78 years and continued to occur in midlife and beyond (including 20% after 65 years of age). Similarly, heart failure–related deaths did not show statistically significant differences among the age groups with respect to occurrence and annual mortality. Only with stroke were differences according to age identified, with significantly increased occurrence of death and annual mortality in the elderly.

We believe that the important differences cited between HCM data sets regarding clinical course are explained largely by patient selection, usually younger and higher-risk patients preferentially referred to tertiary centers.^{21,22} When such selection bias is removed (as in the present study cohort), the clinical profile of sudden death is considerably altered, emphasizing that patient referral patterns are probably the

strongest determinants of our prevailing perceptions regarding the clinical expression and impact of HCM.^{1,6,7,22}

Our observations that sudden death in HCM is not limited to young patients and that the risk period in this disease extends virtually throughout life have important clinical implications. Such revised perceptions are relevant to risk stratification and treatment for the prevention of sudden cardiac death, particularly with respect to the potential role of the ICD in this disease.³⁵ Indeed, in contrast to coronary artery disease,³⁶ patients with HCM are often much younger (average, 40 years of age) and have long periods of potential risk when regarded as candidates for the primary prevention of sudden death.³⁵

We are uncertain about the potential impact that the administration of amiodarone to a segment of the patient population had on our findings. It has been suggested that amiodarone may be protective against sudden cardiac death in HCM,^{37,38} and $\approx 15\%$ of the patients in this study population received this drug prophylactically. However, an important observation of this study is that $\approx 15\%$ of our patients who died suddenly were treated with amiodarone (usually 200 mg/d), clearly demonstrating that the administration of this drug is not absolutely protective against the risk for arrhythmic death.³⁷ Furthermore, the finding that only $\approx 10\%$ of those patients treated with amiodarone developed progressive heart failure–related death confirms our suspicion that administration of this drug probably does not predispose to cardiac death in HCM.³⁸

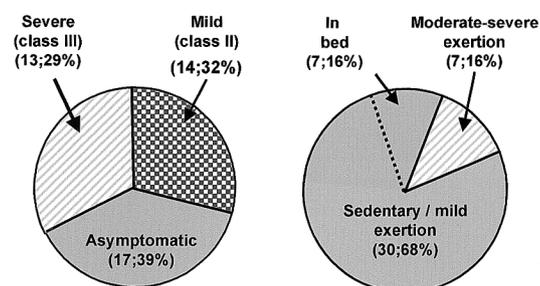


Figure 4. Clinical profile of sudden death. Symptomatic state before death based on NYHA functional class (left) and activity level at time of collapse (right) in 44 HCM patients who died suddenly (or survived cardiac arrest or had appropriate ICD interventions).

TABLE 2. Continued

LVED, mm	LA, mm	With AF, n (%)
42±7 (22–60)	42±10 (27–80)	14 (32)
42±8 (26–56)	52±10§ (38–65)	17 (55)
41±6 (29–52)	47±8 (28–56)	10 (91)¶#

We identified a relatively low frequency of sudden deaths (or cardiac arrest) occurring during or just after moderate to severe physical exertion ($\approx 15\%$). These observations contrast somewhat with the data assembled in highly selected HCM tertiary referral institutions that included patients without prior clinical evaluation initially identified at autopsy.²¹ First, it should be emphasized that none of the patients in the present consecutive population were known to be trained competitive athletes (although 1 patient died while engaged in sports). Second, our reduced frequency of exertion-related sudden death probably reflects the current widespread awareness of risks for young HCM patients engaged in intense sports,^{39–43} as well as the changing attitudes and recommendations against competitive athletics for such individuals.^{39–42,44} Third, the vast majority of athletes with HCM who die suddenly are not aware of their underlying disease and therefore would not be likely to appear in a consecutively diagnosed and enrolled cohort such as the present one. Indeed, we cannot be certain how many additional patients in this generally low-risk cohort would have died had they been systematically exposed to an athletic lifestyle. Consequently, the present data should not undermine the well-established link between intense competitive sports and the risk for sudden death with HCM.^{39,40,44}

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